CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-456/458

APPROVED DRAFT LABELING

Skie: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensrivity; Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes,

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renai Isaliure, oliguris, renai dystunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), urinary tract infection, flank pain, gyreconastis, impotence. Miscrellaseeus: A symptom complex has been reported which may include some or all of the following: a positive ARA, an elevited erythrocyte sedimentation rate, arthralgia/arthritis, maylea/myssits, lever, serseistis, vasculidis, leukocytosis, eseanophilia, photoseansitivity, ranain and other dermatologic manifestations. Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension, and other orthostatic effects) was reported in 2.3 percent of patients (following the initial does of enalaprid or during artended therapy. In the hypotensione patients, hypotension occurred in 0.9 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. (See WARNINGS.) Fatal/Neonatal Morbidity and Mortality.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.
Clinical Laboratory Test Findings
Serum Electrolyze: Hyperkalemia (see PRECAUTIONS), hyponatremia.
Creatinine, Blood Urea Nitrogen: In controlled Chinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2 percent of patients with essential hypertension treated with enalapiti alone. Increases are more kiledy to occur in patients receiving concomitant districts or in patients with renal artery stemosis. (See PRECAUTIONS.)

Hematology: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalapis but are resely of chinical importance unless another cause of anemia co-exists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia. Hemolytic anemia, including cases of hemolysis in patients with 6.6-P0 deficiency, has been reported; a causal relationship to enalapir cannot be excluded.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Failure).

OVERDOSAGE

WARNING, Repair Failure.

VOYENDOSAGE
In clinical studies, some hypertensive patients received a maximum dose of 80 mg of enalagriatin intrevenously over a fifteen manute period. At this high dose, no adverse effects beyond those as associated with the recommended dosages were observed.

A single intravenous dose of 54167 mg/ng of enalagriat was associated with lethality in famale mice. No lethality occurred after an intravenous dose of 3472 mg/ng.

The most lately manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Enalagriat may be removed from general circulation by hemodistysis and has been removed from neonatal circulation by peritoneal disrysis. (See WARNINGS, Anaphylactoid Reactions During Membrane Exposure).

OUS.AGE AND ADMINISTRATION FOR NORMANDISTRATION ONLY.

The dose in hypertension is 1.25 mg every six hours administered intravenously over a five munitup period. A chinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing. The peak effects of the sacond and subsequent doses may acceed those of the first.

No dosage regimen for enalagriat injection has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every xix hours. However, in controlled clinical studies in hypertension, doses as high as 5 mg every six hours therewer, in controlled clinical studies in hypertension, doses as high as 5 mg every wix hours there and ministrate for day.

clinical studies in hypertension, doses as high as 5 mg every six hours were well tolerated for up to 38 hours. There has been inadequate experience with doses greater than 20 mg per day.

In studies of patients with hypertension, enalsprilat injection has not been administared for periods longer than 48 hours. In other studies, patients have received enalsprilat injection from oral therapy for hypertension with enalspril maleate is 1.25 mg every six hours. For conversion from intravenous to oral therapy, the recommended initial dose of finalspril Maleate Tablets is 5 mg once a day with subsequent dosage adjustments as necessary.

Patients on Biuretic Therapy the recommended starting dose for hypertension is 0.825 mg administered intravenously over a five minute period; also see below, Patients at Risk of Excessive Hypotension. A clinical response is usually seen without 15 minutes. Pask effects after the first dose may not occur for up to four hours after dosing, athough most off the effect is usually apparent within the first hour. If after one hour there is an inadequate clinical response, the 0.825 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of Enalapril Maleate Tablets for patients who have responded to 0.625 mg of enalaprilat every six hours is 2.5 mg once a day with subsequent dosage adjustment as necessary.

Design Afglustment is Reseal tengal mean recommended for patients with a creations clearance > 30 mL/min (serum creations clearance > 30 mL/min (serum creations) and patients at a necessary.

Design Afglustment is Reseal tengal mean recommended for patients with a creations clearance > 30 mL/min serum creations clearance > 30 mL/min serum creations clearance > 30 mL/min feature reponded.

For conversion from intravenous to oral therapy, the 0.825 mg (See WARNINGS).

For dialysis patients, see below, Patients at Risk of Excessive Hypotension.

For conversion trom intraven

Administration
Enalignifal injection should be administered as a slow intravenous infusion, as indicated above. It may be administered as provided or diluted with up to 50 mL of a compatible diluent. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever soution and container permit. Compatibility and Stability
Enalagnital fluction as supplied and mixed with the following intravenous diluents has been found to maintain full activity for 24 hours at room temperature:

Special Dattrose Injection
03 percent Sodium Chloride Injection
03 percent Sodium Chloride Injection in 5 percent Destrose in Lactated Ringer's Injection
McGaw ISOLYTE***[C. McGaw ISOLYTE**]

McGaw ISOLYTE***[C. McGaw ISOLYTE**]

McGaw ISOLYTE***[C. McGaw ISOLYTE**]

HOW SUPPLIED

List	Centainer	Concentration	Fijl	Quantity
2109	Carpuject® 22 Gauge, 1% Needle	1.25 mg/mL	1 mL	10 per Box
2109	Carpulect ^e Luer Lock	1.25 mg/mL	1 mL	10 per Box
2109	Carouect® Blunt Cannula	1.25 mg/mL	1 mL	10 per Box
2122	Vial	1.25 mg/mL	1 mL	I per Box
2122	Vial	1.25 mg/mL	2 mL	I per Box

Store at 25°C (77°F), excursions permitted 15-30°C (59-86°F).

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USE IN PREGNANCY

When used in pregnency during the second and third trimesters. ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Enaloguist Injection should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Morality.

UZSCRIPTION
Enelaprilat Injection is a sterile aqueous solution for intravenous administration.
Enalaprilat is an angiotensin converting enzyme inhibitor. It is chemically described as (5)-1(A/1-carboxy-3-phenylpropyl)-1-alanyl)-1-proline dihydrate. Its molecular formula is
C_uH_uN₂O₄ > 2H₂O and its structural formula is:

Enalaprilat is a white to off-white, crystalline powder with a molecular weight of 384.43. is spanioply soluble in methanol and slightly soluble in water. Each milliliter contains 1.25 mg enalaprilet (anhydrous equivalent); sodium chloride to djust tonickly, benzyl sicohol, 9 mg, added as a preservative. May contain sodium hydroxide

CHANCAL PHARMACOLOGY

for pit adjustment.

CLINICAL PHARMACOLOGY

Enalagrilat, an angiotensin-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolise of the orally administered pro-drug, enalagril malease. Enalagrilat poorly absorbed orally.

Mechanism of Action

Intravenous analagrilat, or oral enalagril, after hydrolysis to enalagrilat, inhibits ACE in human subjects and animals. ACE is a peptidy dipaptidase that catalyzes the conversion of angiotensian I to the vasoconstrictor substance, angiotensia II. Angiotensic II also stimulates addoctarones sacretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensian II, which leads to decreased vasopressor activity and to decreased plasma angiotensian II, which leads to decreased vasopressor activity and to decreased adoptations accretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalagril alone for up to 45 weeks, mean increases in serum potassium of approximately 0.2 mG/d, were observed, in patients treated with enalagril plus a thiazide diuretic, there was essentially no change in serum potassium. (See PRECAUITONS.) Removal of angiotensian II negative feedbact on renin secretion leads to increased plasma renin activity.

ACE is identical to kinnase, an enzyme that degrades bradykinin. Whether increased levels of fradykinin, a potent vasodegressor peptide, play a role in the therapeutic affects of enalagrilat remains to be elucidated.

While the mechanism through which enalagrilat lowers blood pressure is believed to be primarily suppressic of the renin-angiotensin-aldosterone system, enalagrilat has antihypertensive activity even in patients with low-renin hypertensive population) had a smaller

primarily suppression of the renin-engiotensin-aldosterone system, enalaprilat has antihypertensive activity even in patients with low-renin hypertension. In chinical studies, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalaprilat monotherapy than non-black patients.

Pharmacelizations and Metabelism
Following intravenous administration of a single dose, the serum concentration profile of enalaprilat is polyexponential with a prolonged terminal phase, apparently representing a small fraction of the administrated dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat, as determined from oral administration of multiple dose of enalapril maleate, is approximately 11 hours. Excretion of enalaprilat is primarily renal with more than 90 percent of an administered dose recovered in the urine as unchanged drug within 24 hours. Enalaprilat is poorly absorbed following oral administration.

more than 90 percent of an administered dose recovered in the urine as unchanged drug within 24 hours. Enalepted is poorly absorbed following oral administration. The disposition of enalepted in patients with renal insufficiency is similar to that in easients with normal renal function until the glomerular filtration rate is 30 mL/mm or less. Writh glomerular filtration rate is 30 mL/mm or less. Writh glomerular filtration rate 530 mL/mm, east and trough enaleptial televal increase, intended to peak concentration increases and time to steady state may be delayed. The effective half-life of enaleptial is prolonged at this level of tenal insufficiency. (See DOSAGE AND ADMINISTRATION). Enaleptials is dialyzable at the rate of 52 mL/min.

Studies in dogs indicate that enaleptial dose not enter the brain, and that enaleptial crosses the blood-basin barrier poorly, if at all. Multiple doses of enalepti maleate in rats do not result in accumulation in any tissues. Milk in lactating rats contains radioactivity following administration of "C enalepti maleate. Radioactivity was found to cross the placents fidewing administration of labeled drug to preparant hamsters.

Pharmacestynamics

Pharmacedynamics
Enslaprilat Injection results in the reduction of both supine and standing systolic and disatolic blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-deplated hypotension is therefore infrequent, although it might be anticipated in volume-deplated of administration with the maximum effect occurring within one to four hours. The abrupt withdraward enaleprists are not been associated with a repoil increase in blood pressure. The duration of hemedynamic effects appears to be dose-clated. However, for the recommended dose, the duration of action is most patients approximately six hours. Following administration of enaleprist, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

MINICATIONES AND USAGE
Enaleprists listences is indicated for the treatment of hypertension when or all therapy is not

Enalaprilat Injection is indicated for the treatment of hypertension when oral therapy is not

craspirate injection has been studied with only one other antihypertensive signification, practical.

Enalaprilat injection has been studied with only one other antihypertensive significations, which showed approximately additive effects on blood pressure. Enalapril, the pro-drug of enalaprilat, has been used extensively with a variety of other antihypertensive agents, without apparent difficulty except for occasional hypotension.

In using Enalaprilat Injection, consideration should be given to the fact that another anoiteness converting enzyme inhibitor, coplopid, has caused agranulocytosis, particularly in patients with renal impairment or collegen vascular disease, and that available data insufficient to show that Enalaprilat Injection does not have a similar risk. ISee WARNINGS. In considering use of Enalaprilat Injection, it should be noted that in controlled clinical traits AEE inhibitors have an effect on blood pressure that is less in black patients than one-blacks in addition, it should be noted that that patients receiving ACE inhibitors have been reported to have a higher incidence of angioedems compared to non-blacks. (See WARNINGS, Angioedems.)

CONTRAINDICATIONS

Enalaprilat Injection is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angeedean erelated to previous treatment with an angiotensin conventing enzyme inhibitor and in patients with hereidiarry or idiopathic

angioedema.

WARNINGS

Hypotension

Excessive hypotension is rare in uncomplicated hypertensive patients but is a possible consequence of the use of enalaprilat especially in severely salityrolume depleted persons such as those treated vigorously with distretics or patients on dialysis. Patients at risk for excessive hypotension, sometimes associated with bilguiris and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics. heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diversite dose, renal dialysis, or severe volume and/or said depletion of any etiology. It may be advisable to eliminate the diuretic, reduce the diuretic dose or increase sait intake cutulously before initing therapy with Enalaprilat Injection in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.) In patients with heart failure, with or without associated with eliquina and/or progressive azotemia, and rarely with acute renal failure and/or efeath. Because of the potential for an excessive fall in blood pressure especially in these patients, therapy should be followed closely whenever the does of enalaprilat is adjusted and/or distretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the suprine position and, in eccessary, receive an intravenous influsion of normal saline. Alt renainent hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Anaphylactoid and Pessibly Related Reactions

Presumably because angiotensin-converting angiven bradythinin, patients receiving ACE inhibitors including Enalaprilat Insection) may be subject to a variety of adverse reactions, s

some of them serious.

Angioedems: Angioedems of the face, extremities, lips, tongue, glottis and/or larynk has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalsprilat. This may occur at any time during treatment, In such cases, Enalsprilat Injection should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although artihistamines have been useful in relaving aymptoms. Angioedema associated with laryngal edems may be fatal. Where there is involvement of the tongue, glottis or laryns, likely to cause sinvay obstruction, appropriate tharapy, aubucutaneses epinophrine solution 1:1000 (0.3 ml. to 0.3 ml.) and/or measures necessary to ensure a patent airway, abaculab be promptly previded. [See ADVERSE REACTIONS.]

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INOICATIONS ANO USAGE and CONTRAINDICATIONS).

increased risk of angioedema while USAGE and CONTRAINDICATIONS).

NCSAGE and CONTRAINDICATIONS.

Anaphylacteid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenopters venom while receiving ACE inhibitors sustained life-threatening anaphylacteid reactions. In the same patients, these reactions were avoided when ACE inhibitors are temporarily withheld, but they reappeared upon inadverter rachallenge. Anaphylacteid reactions are temporarily withheld. But they reappeared upon inadverter rachallenge. Anaphylacteid Reactions During Membrane Expessive: Anaphylacteid reactions have been reported in patients dialyzed with high-flux membranes and treated concentivative with an ACE inhibitor. Anaphylacteid reactions have also been reported in patients undergoing low-density Reported aphresis with dextran sulfate absorption.

Neutropenia/Agramulecyteais
Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agramulocytesis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available date from clinical trials of enalpair is insufficient to show that enalpaird does not cause agranulocytesis in mimilar rates. Marketing experience has revealed cases of neutropenia, or agranulocytesis in mimilar rates. Marketing experience has revealed cases of exceptions or agranulocytesis in which a causal relationship to enalpair cannot be accided. Periodic monitoring of white blood call counts in patients with collegen vascular diseases and renal disease should be considered.

accined. Periodic monitoring of white blood cell counts in patients with collegen vascular disease and read disease should be considered. Hegatic failure Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaurdice and progresses to fulminant hepatic necrosis, and (sometimes) death. The machanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up. ACE inhibitors can cause fatal and meonstal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fatal and neonatal injury, including hypotension, neonatal stuff hypoplasis, anuris, reversible or irreversible renal faiture, and death. Disjohydramnios has also been reported, presumably resulting from decreased feate renal function; disjohydramnios has also been theyoff and the second pregnancy of the patient ducture arteriosus have also been reported, atthough it is not clear whether these occurrences were due to the ACE-inhibitor suposure. These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor apposure that has been limited to the first trimester. Mothers whose embryor* and fetuses are exposed to ACE inhibitors only during the first trimester. Mothers whose embryor* and fetuses are exposed to ACE inhibitors only during the first trimester. Mothers whose embryor* and fetuses are exposed to ACE inhibitors only during the first trimester. Mothers whose embryor* and fetuses are exposed to ACE inhibitors and during the first trimester. Mothers whose embryor* and fetuses are exposed to ACE inhibitors and during the first trimester.

are exposed to ACE inhibitors only during the first trimester should be so informed. Monetheless, when patients become pregnant, physicians should make every effort to discontinue the use of Enalaprilat Injection as soon as possible. Alzely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these area cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to

potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligiophyframnios is observed, Enalaprilat Injection should be discontinued unless it is considered lifeaving for the mether. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be sware, however, that oligiphyframios may not appear until after the fetus has sustained irreversible injury.

Intants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, ofiguris, and hyperkalemia. If oligiuris accure, attention should be directed toward support of blood pressure and renal partusion. Exchange transition or disyste may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placents, has been removed from neonatal circulation by perfoneal dialysis with some chinical benefit, and theoretically may be removed by exchange transitions, although there is no experience with the latter procedure.

No teratogenic effects of oral enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

PRECAUTIONS

General

Aortic Stenosis/Hypestrophic Cerdiomyopethy: As with all vasodilators, enalapril should be

General
Agric Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, enalapril should be
given with caution to patients with obstruction in the outflow tract of the left ventricle.
Impaired Renal Function: As a consequence of inhibiting the renin-engintensia-aldosterone
system, changes in renal function may be anticipated in susceptible individuals. In patients
with severe heart failure whose renal function may depend on the activity of the reninangiotensia-aldosterone system, treatment with angiotensia converting enzyme inhibitors,
including enalapril or enalaprilat, may be associated with oliguria and/or progressive
azotemia and rarely with acute renal failure and/or death.

In clinical studies in bypertensive patients with undsteral or bilateral renal artery stensiss, increases in blood urea introgen and serum creatience were observed in 20 percent of patients receiving enalapril. These increases were almost always reversible upon discontinuation of enalapril or enalaprilat and/or discretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood uree and serum creationine, usually minor and transient, especially when enalaprilat has been given concomitantly with a disvetic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalaprilat and/or discontinuation of the disretic may be required.

Evaluation at the hypertensive patient should always include assessment of renal function. (See DIOSAGE AND ADMINISTRATION.)

Hyperkalemie: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients highly account of the patients of characteristic continual therapy. Hyperkalemia was a cause of discontinuation of therapy in CS percent of hypertensive patients. Risk factors for the development of hyperkalemia include renal insulficiency, diabetes mellitus, and the concomitant use of potassium-sparing agents or petassium patients in Characteris which should be used cautiously, if st all, with Enalaprilat Injection. (See Drug Interactions.)

Interactions.)
Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin,
persistent nenproductive cough has been reported with all ACE inhibitors, always resolving
after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the

differential diagnosis of cough.

Surgery/Anesthesis: In patients undergoing major surgery or during anesthesis with agents that produce hypotension, enalapril may block angiotensin It formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

mechanism, a can be corrected by volume expansion.

Drug Interactions

Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in
Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in
whom diuretic therapy was recently instituted, may occasionally experience an excessive
reduction of blood pressure after initiation of therapy with enalaprilat. The possibility of
hypotensive effects with enalaprilat can be minimized by administration of an intravenous
infusion of normal saline, discentinuing the diuretic or increasing the salt intake prior to
initiation of treatment with enalaprilat. If it is necessary to continue the diuretic, provide
close medical supervision for at least one hour after the initial dose of enalaprilat. (See
WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of Enalaprilat Injection appears

to be sugmented by antihypertensive agents that cause renin release (s.g., divertics). Non-steroidel Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril may result in a further deterioration of renal function. These effects are usually

who are being treated with non-steroidal anti-inflammatory drugs, the co-amministration or enallyrid may result in a further deterioration of renal function. These effects are usually evectedle.

Other Cardiovascular Agants: Enalsprilat Injection has been used concernitantly with digitatis, beta advancept-blocking agents, methyldoga, ndrates, calcium-blocking agents, hydralatine and prazen without evidence of clinically significant adverse interactions. Agents Increasing Serum Protassium inspirilat Injection attenuets potassium loss caused by thizade-type diuretics. Potassium-sparing diuretics (e.g., spironolactions, triamterene, or amiloride), potassium autoplements, or potassium-conclaining ask substitutes may lead to significant increases in serum petassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypotalenia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving kithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalagini and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum tithium levels be monitored frequently if enalagini is administered concomitantly with kithium.

Carcinogenesis, Meusenesis, Impairment of Fertility
Carcinogenesis, Museuments, Impairment of Fertility
Carcinogenesis, Museum

male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis). Pregnency Pragnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fatal/Neonatal Morbidity and Mortality. Mursing Methers Enalapril and enalaprilat have been detected in human breast milk. Because of the potential for serious adverse reactions in nursing infants from enalapril, a decision should be made whether to discontinue nursing or to discontinue Enalaprilat Injection, taking into account the importance of the drug to the morther. Pediantic Uses

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Enalaprilat Injection has been bound to be generally well tolerated in controlled clinical trials involving 349 patients (168 with hypertension, 153 with congestive heart failure and 28 with coronary artery disease). The most frequent clinically significant adverse experience was hypotension (14) percent), occurring in eight patients (52) percent) with congestive heart failure, three (1.8 percent) with hypertension and one with coronary artery disease. Other

failure, three (1.8 percent) with hypertension and one with coronary artery disease. Other adverse experiences occurring in greates than one percent of patients were: headache (2.9 percent) and natures (1.1 percent).

Adverse experiences occurring in 0.5 to 1.8 percent of patients in controlled clinical triats included: myocardial inferction, fatigue, dizziness, fever, rash and constitution. Angliedesma: Angloedema has been reported in patients receiving enalignfals, with an incidence higher in black than in one-black patients. Angloedema associated with larnness adeas may be fatal. If angloedema of the face, extremities, lips, tongue, glottis and/or laryux occurs, treatment with enalignfals should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Cenglis See PRECAUTIONS, Cough.

Enalignt Melacete

Exaleptit Melecete

Since analagrii is converted to enalagrilat, those advarse experiences associated with
enalagria might also be expected to occur with Enalagrizat Injection.

The following advarse experiences have been reported with enalagril and, within each
category, set isted in order of decreasing severity.

Body &A Whele: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS,
Anaphylactoid Reactions During Membrane Exposure), chest pain, abdominal pain, asthematic
Cardisvasculer: Cardiac arrest myocardial interction or cerebrovascular accident, possibly
ascondary to excessive hypotension in high risk patients Isee WARNINGS, Hypotension!,
pulmonary embolism and infaction; pulmonary edems; rhythm disturbances including atrial
tachycardia and bradycardia: strial fibrillation; orthostatic hypotension; angina pectoris;
palpitation, Rayawaid a phenomemen.

sumpt, serverus and orangearas area northables, criticallate hypotension; angina pectoris; pajoistion, Rayanud's phenomenon.
Bigestive: Heus, pancreatitis, hepatic failure, hepatitis (hepatocallular (proven on rechallenge) or chelestatic joundice) (see WARNINGS, Hepatic Failure), melena, diarrhea, vomiting, dyspepsia, ancrexia, glossitis, stomatitis, dry mouth.
Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.
Misszerbeateleai: Muscle cramps.

Masseeleskaletal: Muscle cramps.

Messeeleskaletal: Muscle cramps.

vertigo, confusion, ataxis, somnolence, insonnia, nervousness, peripheral neuropathy (a.g., paresthesia, dysasthesia), dream abnormality. Respiratery: Bronchospasm, dysarea, pnaumonia, bronchist, cough, shinorihea, sore thoat and hoarseness, astima, upper raspiratory infection, pulmonary infiliates, estamophilic



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with Luer Lock

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NDC 0074-2109-31

Enalaprilat Injection

1.25 mg/mL

For I.V. use only.

 \mathbf{R} only



APPROVED

/ AUG 2 2 2000

1 mL

Carpuject® with Luer Lock

Enalaprilat Injection 1.25 mg/mL

Each mL contains: enalaprilat (anhydrous equivalent), 1.25 mg; sodium chloride to adjust tonicity; benzyl alcohol, 9 mg, added as a preservative. May contain sodium hydroxide for pH adjustment.

Usual dosage: See insert.

Store at 25°C (77°F) excursions permitted 15° to 30°C (59° to 86°F).

Enalaprilat Injection

Abbott Laboratories, North Chicago, IL 60064, USA

08-6184-2/RI-11/66



Enalaprilat Injection

Carpujecte with Blunt Cannula

7W1 @



NDC 0074-2109-11 **CE20**

10 Carpuject® Sterile Cartridge Units

with Blunt Cannula

DETECTO-SEAL® PAK Tamper Detection Package

Enalaprilat Injection 1.25 mg/mL

For I.V. use only.

 \mathbf{R} only



Carpuject® with Blunt Cannula

APPROVED AUG 22 2000

1 mL

Carpuject® with Blunt Cannula

Enalaprilat Injection

1.25 mg/mL

Each mL contains: enalaprilat (anhydrous equivalent), 1.25 mg; sodium chloride to adjust tonicity; benzyl alcohol, 9 mg, added as a preservative. May contain sodium hydroxide for pH adjustment.

Usual dosage: See insert.

Store at 25°C (77°F) excursions permitted 15° to 30°C (59° to 86°F).

Enalaprilat Injection 1.25 mg/mL

Abbott Laboratories, North Chicago, IL 60064, USA

08-6183-5\81-11\66



Carpuject® with Blunt Cannula

TO CLOSE INSERT FLAP INTO CARTON TO OPEN LIFT FLAP

1.25 mg/mL Enalaprilat Injection

Carpujecte (22-Gauge, 1%" Needle)

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THIS END UP

Enalaprilat Injection

己 1 mL

NDC 0074-2109-01 **E200**

10 Carpuject® Sterile Cartridge Units (22-Gauge, 1½" Needle)

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Enalaprilat Injection

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Enalaprilat Injection

Carpuject* (22-Gauge, 11/2 Needle)

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08-5185-5/81-11/66



Carpuject* (22-Gauge, 1%" Needle)

O.5 mL mt. 1.5 mL 2 m NDC 0074-2109-01 mt. Carpuject® Stande Cartridge Unix (22-Gauge, 11/4") NDC 0074-2109-01 mt. 25 mg/mL B. only
For I.V. use only.
Abbott Laboratones, N. Chicago, IL 60064, USA
APPROVED

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pamphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing,

disphorasis, photosensitivity. Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes,

Special Senses: Burrad vision, taste atteration, snosma, tinnitus, conjunctivitis, ony eyes, tearing.
Urogenitat: Renal failure, oliquira, renal dysfunction (see PRECAUTIONS and OOSAGE AND ADMINISTRATION), urinary tract infection, flank pain, quescomastia, impotence.
Miscalleneeus: A symptom complex has been reported which may include some or all of the following: a positive ANA, an elevated erythocyte sedimentation rate, arthalgicalarthrists, myalgia/myositis, lever, serositis, vasculitis, leukocytosis, easamophilia, photosensitivity, rash and other dermatologic manifestations.
Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension, and other orthostatic effects) was reported in 2.3 percent of patients following the sinital does of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9 percent and syncops occurred in 0.5 percent of patients. Hypotension or syncops was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. (See WARNINGS.) Fetal/Neonatal Morbidity and Mortality. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Pstat/Noonatal Morbidity and Morbility. See WARNINGS, FetaVNeonatal morbidity and Morbidity.

Clinical Laboratory Test Findings.

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremis.

Creatinine, Blood Uses Nirgogen: in controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2 percent of patients with essential hyperiension treated with snatagrial alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. [See PRECAUTIONS.]

Hematology: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalagric but are rearrely of clinical importance unless another cause of anemia co-exists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia. Hemotytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported, a causal relationship to enalagric cannot be excluded.

ther Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Failure).

WARNINGS, Repatic Failurie.

DVERDOSAGUE*

In clinical studies, some hypertensive patients received a maximum dose of 80 mg of enalagriat intravenously over a fifteen minute period. At this high dose, no adverse effects beyond those as associated with the recommended dosages were observed.

A single intravenous dose of 54167 mg/g of enalagriat was associated with lethality in female mice. No lethality occurred after an intravenous dose of 3472 mg/g.

The most likely manifestation of overdages would be hypotension, for which the usual treatment would be intravenous intuision of normal saline solution.

Enalagriat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis. (See WARNINGS, Anaphylactoid Reactions During Membrane Exposure.)

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS ADMINISTRATION ONLY

The dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. A chinical response is usually seen within 15 minutes. Peak affects after the minute period. A chinical response is usually seen within 15 minutes. Peak affects after the No dosage regismen for enalagriats injection has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every six hours. Nowever, in controlled for up to 35 hours. There has been inadequate experience with dosag greater than 21 mg per 49.

effective in treating hypartansion than 1.25 mg every six hours. However, in controlled clinical studies of patients with hypertension, doses as high as 5 mg every six hours were well tolevated for up to 36 hours. There has been inadequate experience with doses greater than 20 mg per day.

In studies of patients with hypertension, enalapritat injection has not been administered for periods longer than 46 hours. In other studies, patients have received enalapritat injection from oral therapy for hypertension with enalaprit maleate is 1.25 mg every six hours. For conversion from hypertension to perform the studies, patients and experience of patients of patients of patients of patients of patients being converted to enalapritat injection from oral therapy for hypertension to prail therapy, the recommended intelligence of Enalaprit Maleate Tablets: 5 mg once a day with subsequent dosege adjustments as necessary.

Patients en Bituretic Therapy the recommended starting dose for hypertension is 0.825 mg administered intrevenously over a five minute period; also see below, Patients at fisic of Excassive Hypotension. A clinical response is usually seen within 15 minutes. Pask effects after the first dose may not occur for up to four hours after dosing, atthough most of the effect is usually apparent within the first hour. If after one hour there is an inadequate chinical response, the 0.825 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of Enalaprid Maleate Tablets for patients who have responded to 0.825 mg of enalapritat every six hours is 2.5 mg once a day with subsequent dosage adjustment as necessary.

Desage Adjustment in Renal Impairment

The usual dose of 1.25 mg of enalapritat every six hours is recommended for patients with a creatinine clearance 30 mL/min (serum creatinine clamine 2 mg/dL), the initial dose of chalaprit Maleate Tablets is 5 mg once a day for patients with creatinine

Administration
Enalagrisal Injection should be administered as a slow intravenous infusion, as indicated above. It may be administered as provided or diluted with up to 50 mL of a compatible diluent. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit.

Compatibility and Stability

Compatibility and Statemery Enalaprilat Injection as supplied and mixed with the following intravenous diluents has been found to maintain full activity for 24 hours at room temperature:

found to maintain the activity he 2 motors at room temperate 5 percent Defunction Chloride Injection 0.3 percent Sodium Chloride Injection in 5 percent Dextrose 5 percent Dextrose in Lactated Ringer's Injection McGaw ISOL

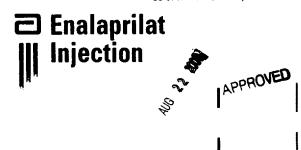
HOW SUPPLIED
Enalaprilat Injection, 1.25 mg per mL, is a clear, colorless solution and is supplied as follows:

List	Container	Concentration	Fill	Quantity
2109	Carpuject® 22 Gauge, 1½" Needle	1.25 mg/mL	1 mL	10 per Box
2109	Carpuject® Luer Lock	1.25 mg/mL	1 mL	10 per Box
2109	Carpulect® Blunt Cannula	1.25 mg/mL	i mL	10 per Box
2122	Vial	i 25 ma/mL	i mL	1 per Box
21.22	16-1	1 36	2	1 and Day

Store at 25°C (77°F), excursions permitted 15-30°C (59-86°F).

***Registered trademark of American Hospital Supply Corporation

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA



USE IN PREGNANCY

use in reconnect.
When used in progesory during the saceed and third trimesters, ACE inhibitors can
cause injury and even death to the developing fetus. When pregnancy is detected,
Enalaprilat Injection should be discontinued as soon as possible. See WARNINGS,
Fetal/Neonatal Morbidity and Mortality.

Englaprilat Injection is a sterile aqueous solution for intravenous administration. Chaispring injection is a turn adjusted enzyme inhibitor. It is chemically described as (Sr.1- $\{M^2_i\}$ -carboxy-3-phenylpropy)]-1-slanyl]-1-proline dihydrate. Its molecular formula is $C_{ij}M_{ij}N_{ij}O_{ij}$ 2 $N_{ij}O_{ij}$ 2 N_{i

Enalaprilat is a white to off-white, crystalline powder with a molecular weight of 384.43. It is sparingly soluble in methanol and slightly soluble in water. Each millitiate contains 1.25 mg enalapriat (anhydrous equivalent); sodium chloride to adjust tonicity, benzyl alcohol, 9 mg, added as a preservative. May contain sodium hydroxide

CLINICAL PHARMACOLOGY

Enalaprilat, an angiotenain-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalaprilat is poorly absorbed orally. Mec

intravenously, is the active metabolite of the orally administered pro-drug, enalepril meleste. Enaleprist is poorly absorbed orally. Mechanism of Action Intravenous enaleprillat, er oral enalepril, after hydrolysis to enaleprilat, inhibits ACE in human subjects and animats. ACE is a peptidy dipeptidase that catalyzes the conversion of angiotension I to the vasoconstrictor substance, angiotension III. Angiotension I so the vasoconstrictor substance, angiotension III. Angiotension I also stimulates sidosterone accretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotension III, which leads to decreased vasopressor activity and to decreased plasma angiotension III, which leads to decreased vasopressor activity and to decreased adosterone secretion. Atthough the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalepril alone for up to 49 weeks, mean increases in aerum potassium of approximately QL mcQL were observed. In patients treated with enalepril plus a thizaide diuretic, there was essentially no change in serum potassium. (See PRECAITONS) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to timinase, an enzyme that degrades bradyhinin. Whether increased levels of bradyhinia, a potent vasodegressor peptide, play a role in the therapeutic effects of enalapriat remains to be elucidated.

While the mechanism through which enalaprilat lowers blood pressure is believed to be primarily suppression of the renia-angiotensia-aldosterone system, enalaprilat has antihypertensive potients (usually a low-renin hypertensive population) had a smaller average response to enalaprilat monotherapy than non-black patients.

Pharmacekinetics and Metabelism
Following intravenous administration of a single dose, the serum concentration placent of enalaprilat is polyacponential with a prolonged terminal phase, apparently representing a small fraction of the administrat

Pharmacceptomers.

Enalsprist Injection results in the reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthestatic component. Symptomatic postural hypotension is therefore intequent, although it might be anticipated in volume-depleted patients (see WARNINGS). The onast of action usually occurs within fifteen minutes of administration with the maximum effect occurring within one to four hours. The abrupt withdrawal of enalsprist has not been associated with a rapid increase in blood pressure.

winner award or enterprise has not open exposers when a rapin whereas in some passers. The duration of hemodynamic effects appears to be dose-related. However, for the recommended dose, the duration of action in most patients is approximately six hours. Following administration of enalspril, there is an increase in renal blood flow, glomerular fittration rate is usually unchanged. The effects appear to be similar in patients with

INDICATIONS AND USAGE
Englaphist Injection is indicated for the treatment of hypertension when oral therapy is not

practical.

Enalagrilat Injection has been studied with only one other antihypertensive agent, furosemide, which shewed approximately additive effects on blood pressure. Enalagril, the pro-drug of enalagrilat, has been used extensively with a variety of other antihypertensive agents, without appeared difficulty except for occasional hypotension.

In using Enalagrilat Injection, consideration should be given to the fact that another ampiotensia converting enzyme inhibitor, captoport, has caused egranulocytesis, particularly in patients with renal impairment or cellagen vascular disease, and that available data are insufficient to show that Enalegrilat Injection does not have a similar risk. (See WARNINGS.) In considering use of Enalagrilat Injection, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in one-blacks. In addition, it should be noted that of the patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

CONTRAINDICATIONS

Comparison to Contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedems related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic

Excessive hypotension is rare in uncomplicated hypertensive patients but is a possible Excessive hypotension is rare in uncomplicated hyportensive patients but is a possible consequence of the use of enalaprils especially in severely salt/volume depleted persons such as those treated vigorously with disuretics or patients on dishysis. Patients at risk for excessive hypotension, sometimes associated with oligoria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose disuretic therapy, recent intensive disression increase in discretic dose, renal disalysis, or savere volume and/or salt depletion of any etiology. It may be a divisable to eliminate the distratic, reduce the distratic dose or increase salt intake cautiously before initiating therapy with Enalaprilat Injection in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS, and DOSAGE AND increase sat intake cautiously before initiating therapy with Enalprilat Injection in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS, and DDSAGE AND ADMINISTRATION.) In patients with heart failure, with or without associated renal insulficiency, excessive hypotension has been observed and may be associated with diguris and/or progressive azotemis, and rarely with acute renal failure and/or death. Because of the potential for an excessive fall in blood pressure especially in these patients, therapy should be followed closely whenever the dose of enalsprilat is adjusted and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or ceresforeascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expension. Anaphylacted and Possibly Related Reactions
Presumably because engictensin-converting enzyme inhibitors affect the metabolism of increasing and polypopholes, including endogenous bradyknin, patients receiving ACE inhibitors including Enalsprilat Injection may be subject to a variety of adverse reactions, some of them serious.

inhibitors (including Enalaprials Injection) may be subject to a variety of adverse reactions, some of them serious. Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin conventing enzyme inhibitors, including enalaprilat. This may occur at any time during treatment. In such cases, Enalaprilat Injection should be promptly discontinued and appropriate therapy and monitoring should be provided until completes and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema essociated with laryngeal edema may be fatal. Where there is involvement to the tongue, glottle provided (See ADVERSE RACTIONS.) Patients with a history of angioedema in 1000 (0.3 mt to 0.5 mt) and/or measures excessory to ensure a patient airway, should be promptly provided. (See ADVERSE RACTIONS.) Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving and ACE inhibitor (see also INDICATIONS AND USABE and CONTRAINDICATIONS as successed risk of angioedema while receiving and ACE inhibitors sustained life-threatening anaphylacticid feactions. In the same patients, these reactions were avoided when ACE inhibitors et amporarily withheld, but they reappeared upon inadverted rechallenge. Anaphylacticid reactions During Membrane Exposurer: Anaphylacticid reactions have been reported in patients dislipate with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylacticid reactions buring Membrane Exposurer: Anaphylactioid reactions along the membrane and treated concomitantly with an ACE inhibitor. Anaphylactiod reactions have been reported in patients undergoing low-density flooprotein apherasis with dexiran sulfate absorption.

leutropenia/Agranulecytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rzrely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of englagril are insufficient to show that enalogril does not cause agranulocytosis in similar rates. Marketing experience has revealed cases of enuloped cases in similar rates. Marketing experience has revealed cases of neutropenia, or agranulocytosis in which a causal relationship to enalgarif cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular diseases and renal diseases should be considered. Repatic Failure

neutropenia, or agranulocytosis in which a causal relationship to enalsprid cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. Heapatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progressas to fulminant hepatic necrosis, and fsometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitors can cause festal and neonatal morbidity and death when administered to pragnant women. Several dozen cases have been reported in the world literature. When pragnancy is detected, ACE inhibitors can cause fishibitors should be discontinued as soon as passible.

The use of ACE inhibitors during the second and third trimesters of pragnancy has been associated with fettal and neonatal injury, including hypotension, neonatal sixty as a sample and a soon as passible.

The use of ACE inhibitors during the second and third trimesters of pragnancy has been associated with fettal induced in the second and third trimesters of pragnancy has been associated with fettal induced to the second and function, oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, oligohydramnios in this setting has been associated with fetal induce contractives, cranifocial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriasus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetues are asposed to ACE inhibitors and but time the first trimester. Mothers whose embryos and fetues are supposed to ACE inhibitors and but the result

maximum recon PRECAUTIONS

General
Anotic Stenois/Hypertrophic Cardiomyopathy: As with all vesodileters, enalapril should be
given with caution to patients with obstruction in the outflow tract of the left ventricle.
Impared Renal Function: As a consequence of inhibiting the renn-angiotensin-aldosterone
system, changes in renal function may be suitcipated in susceptible individuals. In patients
with severe heart failure whose renal function may be susceptible individuals. In patients
with severe heart failure whose renal function may depend on the activity of the reninangiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors,
including enalapril or enalaprilat, may be associated with oliguria and/or progressive
azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with waitsteral or bideteral renet arrany stenosis, increases in blood urea natrogen and serum creatinine were observed in 20 percent of patients receiving enalagrii. These increases were almost always reversible upon discentinuation of enalagrial or enalagrial and/or diviertic therapy. In such patients renal function should be monkored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalagrials has been given concomitantly with a divietic. This is more likely to occur in patients with pre-existing renal impairment. Disage reduction of enalagrials and/or discontinuation of the divircit may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSADE AND ADMAINSTRATION.)

function. (See DUSALE AND ADMAINS IN A HUM.)

Hyperkalemis: Elevated serum potassium (greater than 5.7 mEg/L) was observed in approximately one percent of hypertensive patients in clinical trials receiving enalaprd. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency diabets mellitus, and the concomitant use of potassium-sparing algents or potassium supplements, which should be used cautiously, if at all, with Enalaprilat Injection. (See Drug

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor induced cough should be considered in the

after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory reain release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

mechnism, it can be corrected by volume expansion. Brug hierarctionan Hypotension—Patients on Diureic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalspritat. The possibility of hypotensive effects with enalspritat can be minimized by administration of an intravenous infusion of normal saline, discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalsprilat. If it is necessary to continue the diuretic, provide close medical supervision for at least one hour after the initial dose of enalsprilat. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of Enalaprilat Injection appears

regards Leading realism reviews. "In enterpretaint which or interpret interpret interpretain appears to be sugmented by ambigopertensive agents that cause reminiselesse (e.g., diuretics). Non-steroidal Arai-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalagrif may result in a further deterioration of renal function. These effects are usually

enalapril may result in a nurther outerroration of the continuation of the continuatio

significant increases in serum possasum. Inverview, in concountant uses or meas agents its indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicky has been reported in patients receiving tithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A lew cases of lithium toxicky have been reported in patients receiving concomitant enalappit and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalappit is administered concomitantly with lithium.

Carcinogenicity studies have not been done with final prilat Injection.

Enalaprilat linjection is the bioactive form of its ethyl store, enalapril maleate. There was no evidence of a tumoripeanic effect when enalapril was administered for 106 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times tim male mice) the maximum recommended human daily dose (MRHOD) when compared on a body surface area basis.

Enslaprilat Injection was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril showed no drug-related changes in the following genotoxicity studies: rec-assay, reverse mutation assay with £. coli, sister chromatid exchange with full production was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril showed no drug-related changes in the following genotoxicity studies: rec-assay, reverse mutation assay with £. coli, sister chromatid exchange with the micromucleus test with mice, and in an in vow cytogenic study using mouse bone marrow. There were no adverse effects on reproductive performance of male and female rats treated with up to 50 mg/kg/day of enalapril (25 times the MRHOD when compared on a body surface area basis). ared on a body surface area basis).

compared on a body surface area basis.

Pregnancy
Pregnancy
Pregnancy
Responses
Respon

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Enalogrizal injection has been found to be generally well tolerated in controlled clinical trials involving J49 patients (188 with hypertension, 153 with congestive heart factor and 28 with coronary attery disease). The most frequent clinically significant adverse experience was hypotension (3.4 percent), occurring in eight patients (5.2 percent) with congestive heart fautre, three (1.8 percent) with hypertension and one with coronary attery disease. Other adverse experiences occurring in greater than one percent of patients were: headache (2.9 percent) and nause 4.1 percent). Adverse experiences occurring in 0.5 to 1.0 percent of patients were: headache (2.9 percent) and nause 4.1 percent.

Adverse experiences occurring in 0.5 to 1.0 percent of patients in controlled clinical trials included: mycardial infarction, fatigue, dizziness, fever, rash and constipation.

Anginedems: Angioedema has been reported in patients receiving enalogrizat, with an inno-lack patients. Angioedema associated with layingeal addens may be fatal. If angioedema at the patients Angioedema associated with layingeal addens may be fatal. If angioedema of the face, extremities, lips, tongue, glottic and/or laryon occurs, treatment with enalogrizat should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Ceegls: See PRECAUTIONS, Cough.

Enalogrization and the second of decreasing severity.

Bedy As A Whale: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure), chest pain, abdominal pain, asthemia.

Cardiovascular: Cardioc arrest myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotensioni) pulmonary embolism and infarction; pulmonary demonstration, and processival patients on patients of the patients. Propose of the patients of the patients of the patients of the patients.

polytition, Rywaud's phenomenon.
Digestivs: Heus, percestitis, hepatic failure, hepatitis (hepatocallular (proven on rechallengs) or cholestatic jaundical (see WARNINGS, Hepatic Failure), melens, diarrhea, vomting, dyspessia, andrexis, glossids, stomatitis, dry mouth.
Hematotegic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.
Musculeskeletel: Muscle cramps.
Musculeskeletel: Muscle cramps,
Nervous Psychiatric: Operassion, vertigo, confusion, ataxia, somnolenca, insomnia, nervousness, peripheral neuropathy (e.g., paresthesis, dysesthesis), dream abnormality.
Respiratory: Fronchespsam, dyspene, pneumenia, bronchist, cough, rhinorhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic oneumannia;

For LV. use only.

Enalaprilat Injection 2.5 mg/mL)

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NDC 0014-5155-05

08-5150-5/81-11/55

NDC 0074-2122-02

□ 2 mL

Enalaprilat Injection

2.5 mg (1.25 mg/mL)

For I.V. use only.

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Printed in USA

Each mL contains: enalaprilat (anhydrous equivalent), 1.25 mg; sodium chloride to adjust tonicity; benzyl alcohol, 9 mg, added as a preservative. May contain sodium hydroxide for pH adjustment.

Usual dosage: See insert. Store at 25°C (77°F) (see insert). NDC 0074-2122-02

□ 2 mL

Enalaprilat Injection

2.5 mg (1.25 mg/mL)

For I.V. use only.

 \mathbf{R} only

Abbott Laboratories. 406 North Chicago, IL 60064, USA 22







4 to 196 to

m t ⊡ Enalaprilat Injection 1.25 mg/mL For 1.4. use only.

NDC 0014-5155-01

08-6186-5/81-11/66

NDC 0074-2122-01

□ 1 mL

Enalaprilat Injection 1.25 mg/mL

For I.V. use only.

Deinand

Each mL contains: enalaprilat (anhydrous equivalent), 1.25 mg; sodium chloride to adjust tonicity; benzyl alcohol, 9 mg, added as a preservative. May contain sodium hydroxide for pH adjustment.

Usual dosage: See insert. Store at 25°C (77°F) (see insert). NDC 0074-2122-01 E201

☐ 1 mL

Enalaprilat Injection

1.25 mg/mL

For I.V. use only

 \mathbf{R} only

Abbott Laboratories North Chicago, IL 60064, USA

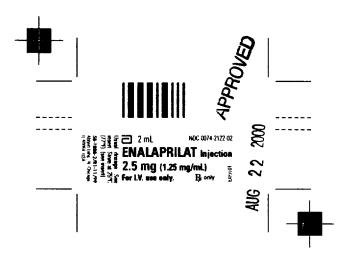


2000

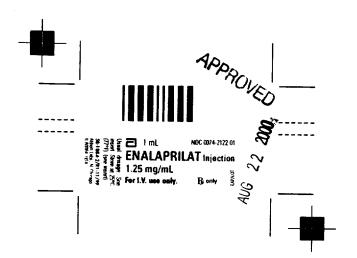
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